Process for the preparation of enantiomerically pure, 2-substituted chroman derivatives

The invention relates to a process for the preparation of enantiomerically pure, 2-substituted chroman derivatives from the corresponding enantiomerically pure chroman-2-carboxylic acid esters.

Enantiomerically pure, 2-substituted chroman derivatives are important intermediates in the preparation of active ingredients for crop protection, such as, for example, fungicides, insecticides, herbicides or pesticides, or of highly pharmaceutically active substances, or are themselves active ingredients of this type.
There is therefore interest in the most economical process possible for the production of these compounds.

The 2-substituted chroman derivative (R)-2-aminomethylchroman, inter alia, is of particular importance as precursor of the CNS-active active ingredient ((R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]chroman). (R)-2-Aminomethylchroman and a number of other 2-aminomethylchroman derivatives are known, for example, from European Patent Application 0 707 007 A1.

((R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]chroman) is an active ingredient having a chiral structure which is used as the pure (R) antipode. Accordingly, the preparation process must be selected in such a way that only the desired antipode can be formed.
The final step in this preparation consists in the conversion of the primary amine 2-aminomethylchroman into the secondary amine ((R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]chroman).
A preferred route for the preparation of the enantiomerically pure end product consists in employing enantiomerically pure (R)-2-aminomethyl-

chroman as precursor since this substance has no enolisable functional groups besides the centre of asymmetry and there is therefore no risk of subsequent racemisation. However, the following of this route requires the availability of the said enantiomerically pure (R)-2-aminomethylchroman.

In the preparation of enantiomerically pure 2-aminomethylchroman, two routes can be followed: either the synthesis is carried out using enantiomerically pure precursors or catalysts, or a racemic synthesis is followed by racemate resolution.

A racemic synthesis starting from N-(4-oxochroman-2-ylmethyl)acetamide is described in WO 02/20507. In a further racemic synthesis, firstly N-(4-oxochromen-2-ylmethyl)acetamide is cleaved using HCl to give 2-aminomethylchromen-4-one, which is then subsequently hydrogenated using Pd/C to give 2-aminomethylchroman. In both cases, the racemic 2-aminomethylchroman can be separated into the two enantiomers by racemate resolution.

Further methods for the preparation of (R)-2-aminomethylchroman are described in WO 00/35901 and in WO 02/088117.

A further conceivable reaction sequence for the preparation of enantiomerically pure 2-aminomethylchroman derivatives starts from the corresponding chroman-2-carboxylic acid esters, which are converted into the corresponding carboxamides. These are either reduced directly to the desired amine or converted, with elimination of water, into the carbonitriles, which are then finally converted into the desired end products by reduction.

This initially attractive-looking synthesis of 2-aminomethylchroman derivatives and other 2-substituted chroman derivatives would, however, not be considered if the preparation of enantiomerically pure products – i.e. retention of the chirality – is important since alkaline reaction conditions (useful ammonia) prevail during this synthesis.

As is known, there is a risk of deprotonation of the carboxylic acid ester, resulting in partial racemisation, under alkaline reaction conditions. The use

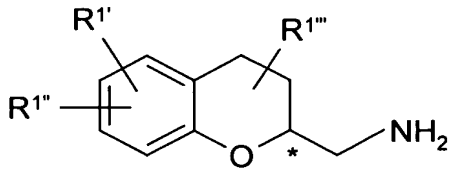
of ammonia for the preparation of enantiomerically pure amide consequently does not appear advisable.

Against expectations, it has now been found by the inventors of the present patent application that the chirality of the enantiomerically pure chroman-2-carboxylic acid esters is retained very well in the reaction with ammonia to give the corresponding carboxamides under alkaline conditions, to the extent that the carboxamides can be obtained with an enantiomeric excess of > 90%.

Likewise surprising is the retention of the chirality during reduction of the carboxamides to the primary 2-aminomethylchroman derivatives since this step is carried out using complex hydrides, such as $LiAlH_4$, and thus likewise under alkaline conditions.
Even the dehydration of the amide to the nitrile, which proceeds under strongly acidic conditions, could result in racemisation with enol formation.

All sub-steps of the process according to the invention are so enantioselective per se that after all sub-steps, i.e. the entire process, have been carried out, an enantiomeric excess of > 90%, preferably > 95%, very particularly preferably > 99%, is always obtained.

The present invention thus relates to a process for the preparation of enantiomerically pure 2-aminomethylchroman derivatives of the formula I



I,

in which the carbon atom labelled with the asterisk is in the (R) or (S) configuration with an enantiomeric excess of > 90% and in which

$R^{1'}$, $R^{1''}$, $R^{1'''}$ each, independently of one another, denotes H, Hal, A, OA, CH_2R^2, NHA, NA_2 or Ar,

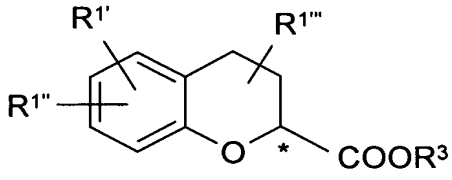
R^2 denotes OA or NA_2,

A denotes unbranched or branched alkyl having 1-10 C atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or by -CH=CH- groups and/or in addition 1-7 H atoms may be replaced by F,

Ar denotes unsaturated, partially or fully saturated, mono- or polycyclic homo- or heterocyclic system containing the hetero atoms O, N, S which is unsubstituted or mono- or polysubstituted by Hal, A, OA or NA_2 and

Hal denotes F, Cl, Br or I,

characterised in that a corresponding (R)- or (S)-chroman-2-carboxylic acid ester of the formula IV

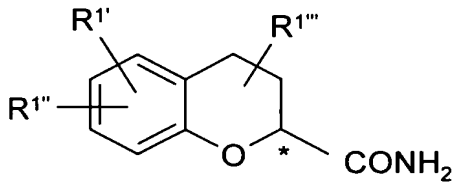


IV,

in which

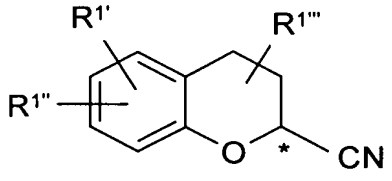
R^3 denotes methyl, ethyl, 1-propyl, isopropyl, 1-butyl, 2-butyl, isobutyl or allyl,

is reacted with ammonia to give a carboxamide of the formula III



III,

which is then dehydrated further to a carbonitrile of the formula II



II,

which is then finally reduced to a compound of the formula I.

The present invention furthermore relates to – as sub-step of the above-mentioned process – a process for the preparation of (R)- or (S)-chroman-2-carboxamides of the formula III with an enantiomeric excess of > 90%, characterised in that a corresponding (R)- or (S)-chroman-2-carboxylic acid ester of the formula IV is reacted with ammonia to give a chroman-2-carboxamide of the formula III.

The above-mentioned radicals preferably have the following meanings:

$R^{1'}$, $R^{1''}$, $R^{1'''}$ each, independently of one another, denotes H, Hal, A, OA, CH_2R^2 or Ar, where A, Ar, Hal and R^2 have one of the meanings described below. $R^{1'}$, $R^{1''}$, $R^{1'''}$ are, in particular, hydrogen, fluorine, alkyl (unbranched or branched having 1-6 C atoms) or alkoxy. $R^{1'}$, $R^{1''}$, $R^{1'''}$ are particularly preferably simultaneously hydrogen.

Hal denotes fluorine, chlorine, bromine or iodine.

R^2 denotes OA or NA_2, where A has the meaning mentioned above and below.

A denotes alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms.
A preferably denotes methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl.
A very particularly preferably denotes alkyl having 1-6 C atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

A furthermore denotes cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or 2,6,6-trimethylbicyclo-[3.1.1]heptyl, but likewise mono- or bicyclic terpenes, preferably p-menthane, menthol, pinane, bornane or camphor, where each known stereoisomeric form is included, or adamantyl. For camphor, this denotes both L-camphor and also D-camphor.

Ar denotes an unsaturated, partially or fully saturated, mono- or polycyclic homo- or heterocyclic system containing the hetero atoms O, N, S which is unsubstituted or mono- or polysubstituted by Hal, A, OA, or NA_2. Preferred cyclic systems are unsubstituted or substituted phenyl, naphthyl or biphenyl, specifically preferably phenyl, o-, m- or p-tolyl, o-, m- or p-methoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p- chlorophenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl.

R^3 denotes methyl, ethyl, 1-propyl, isopropyl, 1-butyl, 2-butyl, isobutyl or allyl, preferably methyl or ethyl. R^3 is particularly preferably methyl or ethyl.

Preferred reactants in the process according to the invention are compounds of the formulae I to IV in which

$R^{1'}$, $R^{1''}$, $R^{1'''}$	each, independently of one another, denote H, F, A, OA,
A	denotes unbranched or branched alkyl having 1-6 C atoms, and
R^3	denotes methyl or ethyl.

In a preferred embodiment of the process according to the invention, the compounds of the formulae I to IV are in the (R) configuration.

A particularly preferred starting material in the process according to the invention is ethyl (R)-chroman-2-carboxylate, which is converted into (R)-2-aminomethylchroman via (R)-chroman-2-carboxamide and further via (R)-chroman-2-carbonitrile.

The present invention therefore likewise relates to the intermediates (R)-chroman-2-carboxamide and (R)-chroman-2-carbonitrile and salts and solvates thereof.

The dehydration according to the invention of the carboxamide to the carbonitrile is preferably carried out using $SOCl_2$, but other suitable dehydration agents, such as, for example, trifluoroacetic anhydride, cyanuric chloride or trimethylsilyl phosphate, can also be employed.

The reaction according to the invention is generally carried out in an inert solvent. Suitable inert solvents for the reactions described above are, for example, hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene, or mixtures of the said solvents.
The amount of solvent is not crucial; in general, 0.5 g to 500 g, preferably 5 g to 100 g, of solvent can be added per g of starting material.

Depending on the conditions used, the reaction temperature for the reactions described above is between about -10°C and 200°C, but normally between -10°C and 100°C.
Depending on the conditions used, the reaction time is between a few seconds and several days, preferably between 1 minute and 24 hours.

For the purposes of this invention, "conditions used" is taken to mean the type and amount of solvent, the type and amount of reagents, the reaction duration, the reaction temperature and further details of the reaction control, such as, for example, the stirrer speed or the other nature of the reac-

tion vessel. However, the substitution pattern of the starting materials is also of importance for the course of the reaction and thus also counts amongst the "conditions used".

In general, the end of the reactions according to the invention is determined by suitable analytical methods, for example thin-layer chromatography or HPLC, and the respective reaction is terminated.
The products and intermediates according to the invention can be obtained by conventional work-up steps, such as, for example, addition of water or acid to the reaction mixture and extraction, after removal of the solvent. It may be advantageous subsequently to carry out a distillation or crystallisation for further purification of the product.

The enantiomerically pure chroman-2-carboxylic acid esters used as starting materials for the process according to the invention are generally known. Thus, for example, EP 0 448 254 A2 describes the preparation of these compounds by racemate resolution using lipases. Should they be unknown, the chroman-2-carboxylic acid esters can be prepared by methods known per se, as described in the literature (for example in standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. However, use can also be made of variants known per se, which are not mentioned here in greater detail.

In general, the procedure below is followed here:

An enantiomerically pure chroman-2-carboxylic acid ester is dissolved in a suitable solvent, such as, for example, methanol, ammonia gas is passed through this solution or an aqueous ammonia solution is added.
After completion of the reaction, the carboxamide separated off from the reaction mixture is dissolved in a second solvent, for example toluene, and

a dehydration agent, such as, for example, thionyl chloride, is added. The carbonitrile obtained here is dissolved in a further solvent, for example methanolic ammonia, and hydrogenated – for example on a solid-phase catalyst, such as Raney nickel – to give the 2-aminomethylchroman according to the invention.
The carbonitrile can optionally also be reduced using another reducing agent (for example $LiAlH_4$, diisobutylaluminium hydride, diborane).

If necessary, the 2-aminomethylchroman can be converted into the corresponding hydrochloride using hydrochloric acid.

For the purposes of the present invention, "enantiomerically pure" is taken to mean an enantiomeric excess of > 90%, preferably > 95%, very particularly preferably > 99%.

In order to protect substituents against undesired reactions during the reduction according to the invention and/or subsequent work-up steps, use is optionally made of protecting groups, which are cleaved off again after reduction of the nicotinic acid morpholinamide. Methods for the use of protecting groups are described, for example, in Theodora W. Green, Peter G. M. Wuts: Protective Groups in Organic Synthesis, 3rd Edition John Wiley & Sons (1999).

Even without further embodiments, it is assumed that a person skilled in the art will be able to utilise the above description in the broadest scope. The preferred embodiments should therefore merely be regarded as descriptive disclosure which is absolutely not limiting in any way.

Examples

1. Preparation of (R)-chroman-2-carboxamide

40.0 g of ethyl (R)-chroman-2-carboxylate are dissolved in 40 ml of methanol. Ammonia gas is passed slowly into this solution at 20 to 40°C until a total of 8.0 g of ammonia have been taken up. The solution is stirred for a further 15 hours, during which a suspension forms. After cooling to 0°C, the solid is filtered off with suction, washed with cold methanol and dried at 50°C under reduced pressure.

The yield is 21.5 g (63% of theory). The enantiomeric purity is greater than 99% e.e.

Reaction monitoring by HPLC, method: stationary phase Chiracel OJ (Chiral Technologies, Exton, USA), mobile phase 90% heptane + 10% isopropanol, flow rate 0.5 ml/minute.

Retention times: (R)-amide = 22 minutes, (S)-amide = 28 minutes

2. Preparation of (R)-chroman-2-carbonitrile

85.0 g of thionyl chloride are added to 105.5 g of (R)-chroman-2-carboxamide from Example 1 in 700 ml of toluene, and the mixture is subsequently warmed at 80°C for 24 hours. After about 200 ml of thionyl chloride/toluene azeotrope have been distilled off, 5% sodium hydroxide solution is added at room temperature until pH 9 has been reached. The aqueous phase is separated off and subsequently extracted with toluene. The combined toluene phases are filtered through silica gel and then evaporated to dryness.

The yield is 92 g (88% of theory). The enantiomeric purity is greater than 99% e.e.

Reaction monitoring by HPLC, method: stationary phase Chiralpak AD (Chiral Technologies, Exton, USA); mobile phase methanol, flow rate 0.5 ml/minute.

Retention times: (R)-amide = 4.04 minutes, (S)-amide = 4.65 minutes

3. Preparation of (R)-2-aminomethylchroman

0.2 g of (R)-chroman-2-carbonitrile from Example 2 are dissolved in 50 ml of methanolic ammonia, 1 g of methanol-moist Raney nickel is added, and the mixture is hydrogenated at 3 bar and 60°C over the course of 10 hours. The catalyst is separated off, the solvent is distilled off, the residue is taken up in ethyl acetate and extracted with dilute sodium hydroxide solution, filtered and evaporated.

The yield of (R)-2-aminomethylchroman is 0.13 g (62% of theory) The enantiomeric purity is greater than 99% e.e.

Reaction monitoring by HPLC, method: stationary phase Chrownpak CR(+) (Chiral Technologies, Exton, USA) 150 mm x 4 mm, column temperature 40°C, mobile phase 90% water + 10% methanol, adjusted to pH 2.0 using HClO4, flow rate 1.2 ml/min.

Retention times: (S)-amine = 11 minutes, (R)-amine = 26 minutes

4. Preparation of (R)-2-aminomethylchroman, hydrochloride

4.8 g of (R)-chroman-2-carbonitrile from Example 2 are dissolved in 50 ml of THF, and 12 g of a 10% $LiAlH_4$ solution in THF are added at -5°C, and the mixture is stirred at this temperature for two hours. The reaction mixture is subsequently carefully hydrolysed using water, the solid is filtered off, and the filtrate is evaporated. The residue is taken up in ethanol, concentrated hydrochloric acid is added, and the crystals are filtered off.

The yield after drying is 3.4 g (57% of theory) The enantiomeric purity is greater than 99% e.e.